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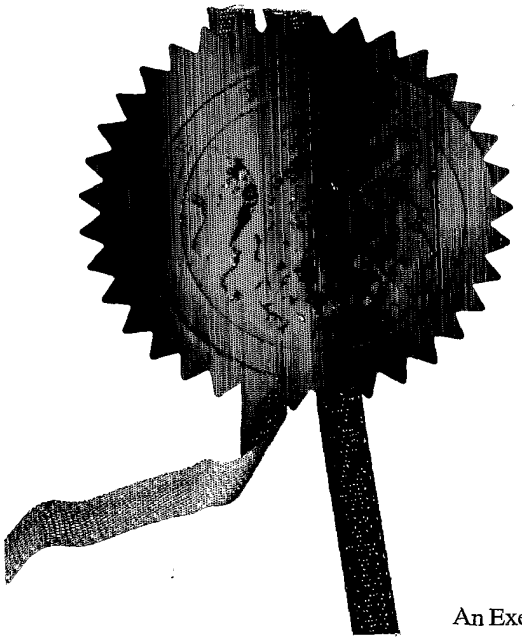

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Dated 14 April 2005

Patents Form 1/77

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1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference

REP07667GB

2. Patent application number
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0406014.1

17 MAR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
Little Chesterford
Saffron Walden
Essex CB10 1XL

Patents ADP number *(if you know it)*

8306128001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Pharmaceutical Composition and Use

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)*

745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	3
Claim(s)	1
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 17 March 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward
020 7377 1377

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Notes

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f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

PHARMACEUTICAL COMPOSITION AND USE

Field of the Invention

This invention relates to a composition of mefloquine and to its use in the treatment of inflammatory disorders.

Background of the Invention

Mefloquine racemate (Lariam) is a known anti-malarial drug. It is typically formulated as a tablet comprising 250 mg of the active ingredient, to be taken weekly. Lariam has well known side-effects.

Bates et al, Int. Arch. Allergy Appl. Immunol. (1998) 86: 446-452, discloses that racemic mefloquine stimulates human neutrophil degranulation. It is reported that mefloquine also inhibits the function of other effector cells that participate in cartilage damage, and that these properties suggest utility as an anti-inflammatory agent. Any such utility would be compromised, in chronic treatment, by the known adverse effects of Lariam, and especially in patients with cardiac disease.

WO02/19994 discloses for the first time that the single enantiomer (+) - erythro-mefloquine is useful in the treatment of chronic conditions, and in particular chronic inflammatory conditions such as osteoarthritis and rheumatoid arthritis. The publication reports that the given enantiomer has greatly reduced side-effects.

Inflammatory conditions have been treated with anti-TNF antibodies. It is known that several patients (as many as 40%) are refractory to this treatment.

Summary of the Invention

The present invention is based at least in part on the realisation that there is a therapeutic window that can be exploited in the treatment of inflammatory conditions, using (+)-erythro-mefloquine. Accordingly, a novel pharmaceutical composition is in the form of a unit dosage comprising 1 to 20 mg (+)-erythro-mefloquine, substantially free of the opposite enantiomer. This dosage form is intended to be taken daily.

The use of (+)-erythro-mefloquine may be particularly valuable in combination with an anti-TNF antibody. Accordingly, such combination therapy constitutes a further aspect of the present invention.

Description of Preferred Embodiments

Despite the fact that mefloquine is associated with a long half-life, the daily dosage proposed according to the invention reduces peaks and troughs in the concentration of the active material. Given this relatively uniform level of drug in the system of the patient being treated, the chances of successful therapy are increased.

The dosage of the active component can be lower than has been associated with the administration of Lariam. The daily dosage according to the invention may be at least 4 mg, and is often no more than 15 mg. A relatively low dosage may be preferable for women.

A desirable aspect of the present invention is the combination with anti-TNF antibodies. This complements the broad, moderate IL-I antagonist activity of (+)-erythro-mefloquine, and can help overcome the problems associated with patients who do not respond to anti-TNF therapy (as described above).

For use in the invention, the active agent may be formulated, e.g. together with a carrier, excipient or diluent, and administered, by procedures that are known in the art, including those already proposed for the racemate. Suitable compositions will depend on the intended route of administration, which may be, for example, oral, topical, nasal, rectal, pulmonary, sublingual, buccal or transdermal. Sustained, delayed, timed or immediate release compositions may be used.

The amount of the agent that should be administered can readily be determined by the skilled man, taking into account the usual factors such as the type of patient, the nature of the condition being treated, and the route of administration. The amount of enantiomer may be higher or the same as that for the racemate, or may be modified depending on the co-administration of other drugs.

Conditions that may be treated include conditions involving cartilage destruction, inflammatory conditions and those mediated by IL-2, IL-6 and II-8, e.g. rheumatoid arthritis, asthma, psoriasis, psoriatic arthritis, Crohn's disease, irritable bowel syndrome and systemic lupus erythematosus. Other relevant conditions are ulcerative colitis, COPD and asthma. The patient may be disposed to CNS side-effects, and/or may be undergoing concomitant therapy with another drug.

The use of (+)-erythro-mefloquine can provide the desired therapeutic effect, without tissue destruction, and can be safely administered at a relatively high dosage. The desired enantiomer of mefloquine may be in at least 50%, 70%, 90%, 95% or 99% excess, with respect to any other. The active agent may be used in any active form, e.g. salt or non-salt.

CLAIMS

1. A pharmaceutical composition in the form of a unit dosage comprising 1 to 20 mg (+)-erythro-mefloquine, substantially free of the opposite enantiomer.

2. A composition according to claim 1, wherein the unit dosage comprises at least 4 mg (+)-erythro-mefloquine.

3. A composition according to claim 1 or claim 2, wherein the unit dosage comprises up to 15 mg (+)-erythro-mefloquine.

4. A composition according to preceding claim, wherein the unit dosage is a tablet comprising a carrier and/or excipient.

5. Use of (+)-erythro-mefloquine for the manufacture of a composition according to any preceding claim, for use in the treatment of an inflammatory condition.

6. Use according to claim 5, wherein the condition is osteoarthritis.

7. Use according to claim 5, wherein the condition is rheumatoid arthritis.

8. Use according to any of claims 5 to 7, wherein the condition is also treated with an anti-TNF antibody.

9. A product comprising (+)-erythro-mefloquine and an anti-TNF antibody, as a combined preparation for simultaneous, separate or sequential use in the treatment of an inflammatory condition.